Electronic Supplementary Material (ESI) for Nanoscale.

Tryptophan Self-assembly Yields Cytotoxic Nanofibers Containing Amyloid-Mimicking and Cross-Seeding Competent Conformers

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Table S1. List of different pathological conditions linked to the fluctuation in *Trp* level in body.

Pathological complications	Tryptophan level	References
Dizziness, nausea, and the illusion of movement in controls to levels that approached those of migraineurs	Decrease Trp in plasma	(Drummond, 2005)
Atherosclerosis	Decrease Trp in serum	(Baldo-Enzi et al., 1996)
Inhibition of indoleamine 2,3-dioxygenase (IDO-1) an Trp catabolising enzyme leads to Atherosclerosis	High Trp	(Ruan et al., 2014)
Alzheimer's disease (AD)	Decrease Trp in plasma	(Porter, Marshall and O'Brien, 2002; Greilberger et al., 2010)
Irritable bowel syndrome (IBD)	Decrease Trp in plasma	(Fitzgerald et al., 2008; Nikolaus et al., 2017; Kałużna-Czaplińska et al., 2019)
Obesity	Decrease Trp in plasma/serum	(Harald Mangge et al., 2014; Strasser, Berger and Fuchs, 2015)
Type 2 Diabetes (T2D)	Increase plasma Trp level	(Oxenkrug, 2015; Chen et al., 2016)
Overweight individuals with bipolar disorder	Decrease Trp level in serum	(Reininghaus et al., 2014)
Anorexia Nervosa	Decrease Trp in CSF and plasma	(Kaye et al., 1988; Gauthier et al., 2014)
Bulimia Nervosa	Increased Trp in plasma	(Kaye et al., 2000)
Autism	Decrease Trp in plasma	(Adams et al., 2011; Naushad et al., 2013)
Parkinson's Disease	Low Trp in CSF	(Widner, Leblhuber and Fuchs, 2002; Naushad et al., 2013)
Sleep Deprivation	Increased Trp in plasma	(Davies et al., 2014)
Fluoxetine treatment	Increase Trp in Brain	(Bano and Sherkheli, 2003)
Oral Trp load	Increase plasma Trp	(Green et al., 1980)
HIV patient	Decrease serum Trp	(Fuchs et al., 1990)
liver cirrhosis/Hepatic coma	Increase Brain/plasma TRP	(Ono et al., 1978; Laviano et al., 1997; Dejong et al., 2007)
Cardiovascular Disease	Decrease Trp in plasma	(H Mangge et al., 2014)
Melanoma	Decrease Trp in plasma	(Weinlich et al., 2007)
Lymphoma	Decrease Trp in plasma	(Suzuki et al., 2010)
Lung cancer	Decrease Trp in plasma	(Engin et al., 2010; Chuang et al., 2014)
Gynecological cancer	Decrease Trp in plasma	(Schroecksnadel et al., 2005)
Gastrointestinal tumors	Decrease Trp in plasma	(Iwagaki et al., 1995)
Colorectal cancer	Serum tryptophan decrease	(Huang et al., 2002)
Breast cancer	Serum tryptophan decrease	(Eniu et al., 2019)
Phenylketonuria (PKU)	Decrease Trp level	(Lou et al., 1985; Smith and Kang, 2000)
Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM)	Decrease Trp in plasma	(Werbach, 2000; Blankfield, 2012)
3,4 methylenedioxymethamphetamine (MDMA) treatment	Decrease Trp in plasma	(Taffe et al., 2003)
Aggressive Behaviour	Decrease Trp in plasma	(Marsh et al., 2002)
Acute Ethanol Consumption	Decrease Trp in plasma	(Badawy et al., 1995)

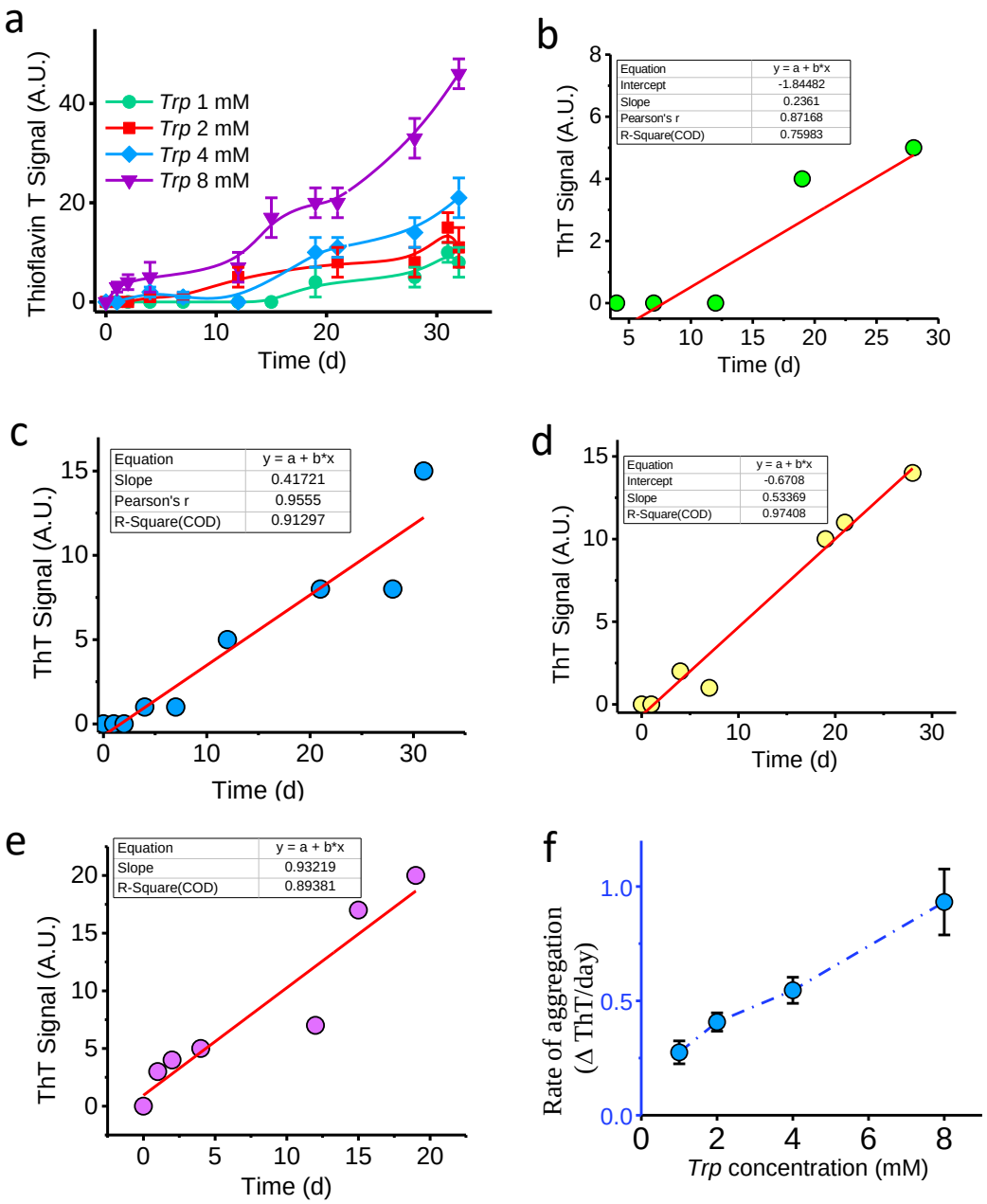


Figure S1. Analysis of the rate of Tryptophan aggregation in a dose-dependent manner. ***a,*** Thioflavin-T data showing dose dependent aggregation of Trp at different concentrations, as labelled. ***b,*** linear fit of initial time points of *Trp* at 1 mM; ***c,*** linear fit of initial time points of *Trp* at 2 mM; ***d,*** linear fit of initial time points of *Trp* at 4 mM; ***e,*** linear fit of initial time points of *Trp* at 8 mM. ***f,*** Plot showing rate of aggregation vs Trp concentration

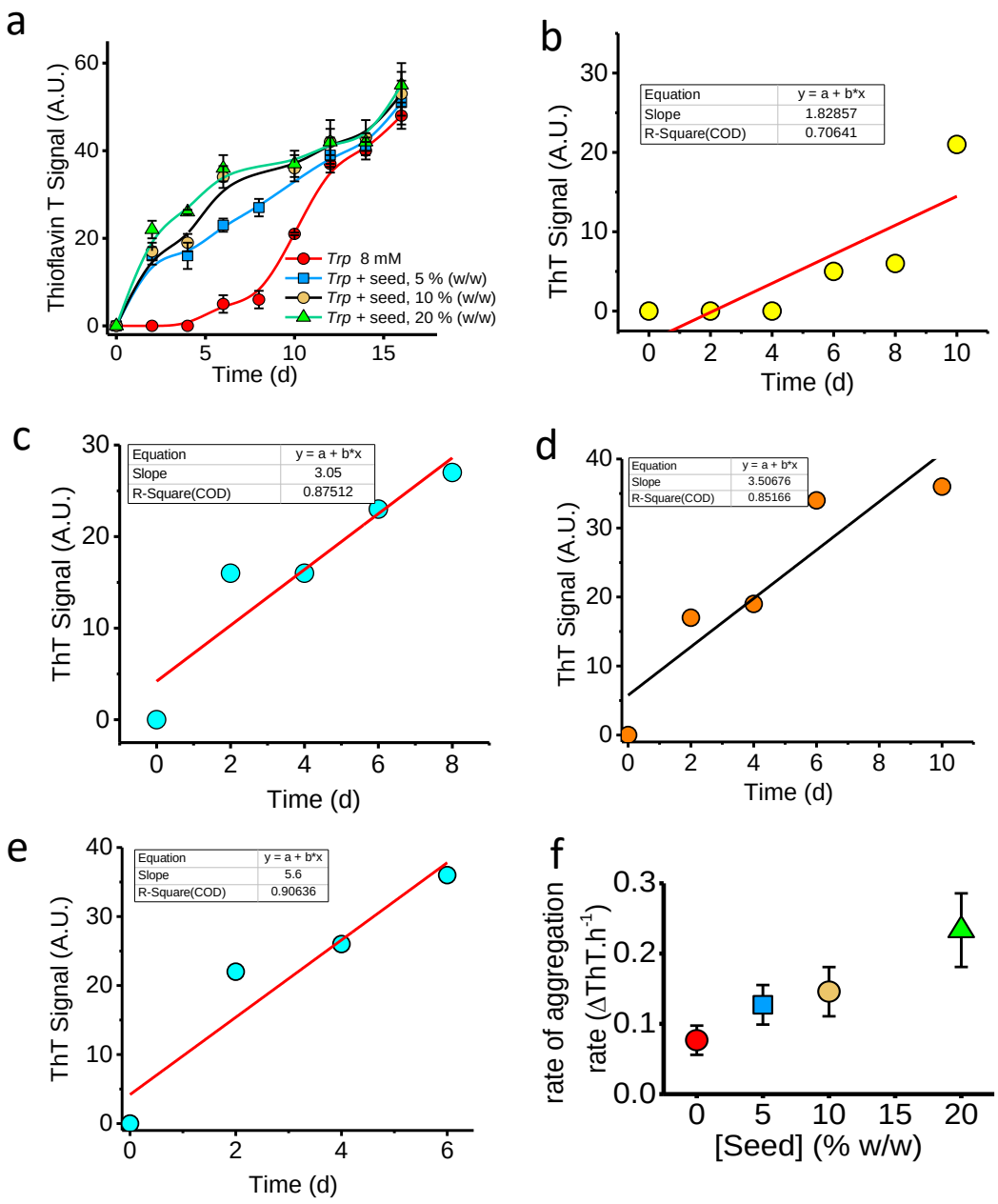
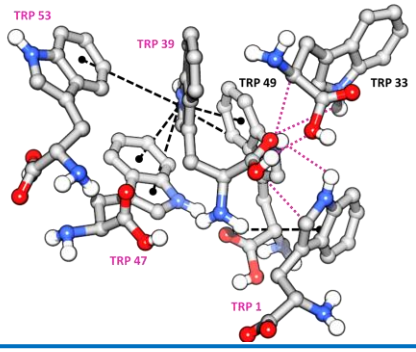


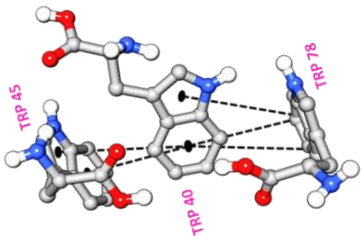
Figure S2. Analysis of the rate of self-seeded aggregation of Trp in dose-dependent manner. ***a,*** Thioflavin-T data showing self seeded aggregation as labelled. ***b,*** linear fit of initial time points of the control aggregation reaction. ***c,*** linear fit of initial time points of the aggregation reaction at 5 % w/w seed of *Trp*. ***d,*** linear fit of initial time points of the aggregation reaction at 10 % w/w seed of *Trp*. ***e,*** linear fit of initial time points of the aggregation reaction at 20 % w/w seed of *Trp*. ***f***, Plot showing the increasing rate of Trp aggregation with increasing seed concentration, as labelled.

a



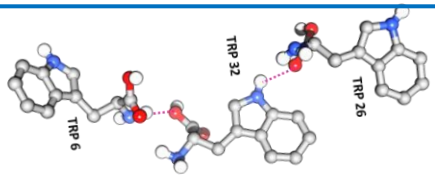
Interacting Residues	Bond length	Type of Interaction
TRP 39 – TRP 53	4.897918	Pi-Pi T-shaped
TRP 39 – TRP 47	4.745665	Pi-Pi T-shaped
TRP 39 – TRP 47	4.570283	Pi-Pi T-shaped
TRP 39 – TRP 49	4.863880	Pi-Pi Stacked
TRP 39 – TRP 49	4.286618	Pi-Pi Stacked
TRP 39:H24 - TRP 55	3.274510	Pi-Donor Hydrogen Bond
TRP 55:H19 - TRP 39:O1	2.661495	Carbon Hydrogen Bond
TRP 55:H20 – TRP 39:O2	2.993630	Hydrogen Bond
TRP 39:H27 – TRP 33:O1	2.012124	Hydrogen Bond
TRP 33:H18 – TRP 39:O2	2.344062	Carbon Hydrogen Bond
TRP 33:H19 – TRP 39:O2	2.266506	Carbon Hydrogen Bond

b



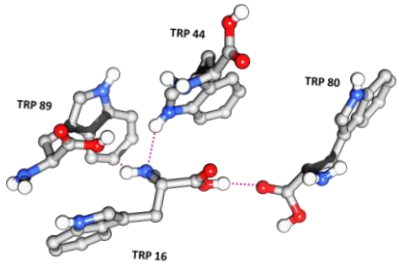
Interacting Residues	Bond length	Type of Interaction
TRP 40 – TRP 78	5.150412	Pi-Pi T-shaped
TRP 78 – TRP 40	5.234781	Pi-Pi T-shaped
TRP 40 – TRP 78	5.172656	Pi-Pi T-shaped
TRP 40 - TRP 45	4.940692	Pi-Pi T-shaped
TRP 45 - TRP 40	5.529468	Pi-Pi T-shaped

c



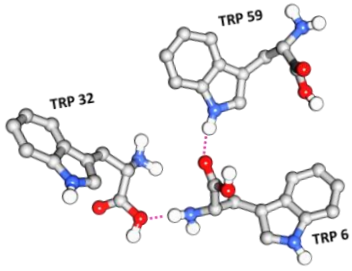
Interacting Residues	Bond length	Type of Interaction
TRP 6:H25 - :TRP 32:O1	1.830516	Hydrogen Bond
TRP 32:H20 – TRP 26:O2	2.495262	Hydrogen Bond

d



Interacting Residues	Bond length	Type of Interaction
TRP16:H27 - B:TRP89:O2	2.628218	Hydrogen Bond
TRP44:H20 - B:TRP16:O2	2.365137	Hydrogen Bond
TRP16:H20 - B:TRP80:O2	1.997695	Hydrogen Bond

e



Interacting Residues	Bond length	Type of Interaction
TRP6:H25 -B:TRP32:O1	1.830516	Hydrogen Bond
TRP59:H20 - B:TRP6:O2	1.944634	Hydrogen Bond

Figure S3. Molecular Dynamic simulation reveals formation of *Trp* nanostructure facilitated by non-covalent interactions. *a-e,* Snapshots of selected portions taken from the simulated *Trp*-nanostructure revealing the intermolecular association between *Trp* molecules via strong non- covalent interactions including H-bonds and π–π interactions between optimally oriented *Trp* molecules, as labelled.

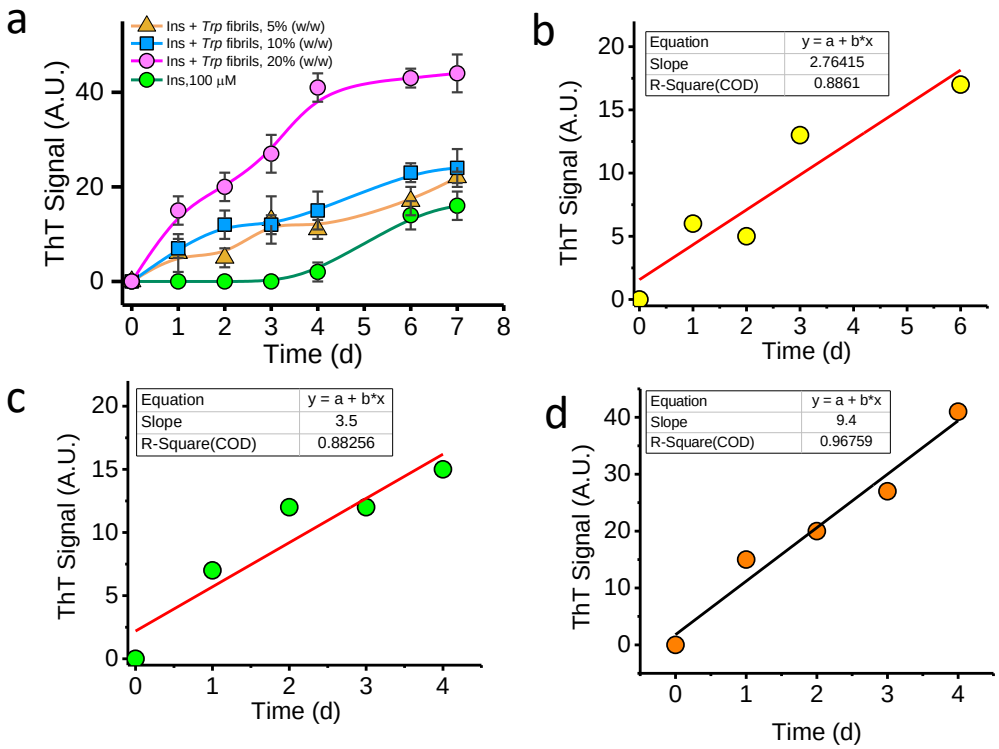


Figure S4. Analysis of the rate of Tryptophan-seeded insulin aggregation at different seed concentrations. ***a,*** Thioflavin-T data showing aggregation of insulin in the presence of different doses of preformed *Trp* seeds, as labelled. ***b,*** linear fit of initial time points of insulin aggregation at 5% (w/w) *Trp* seed. ***c,*** linear fit of initial time points of insulin aggregation at 10% (w/w) *Trp* seed. ***d,*** linear fit of initial time points of insulin aggregation at 20% (w/w) *Trp* seed.

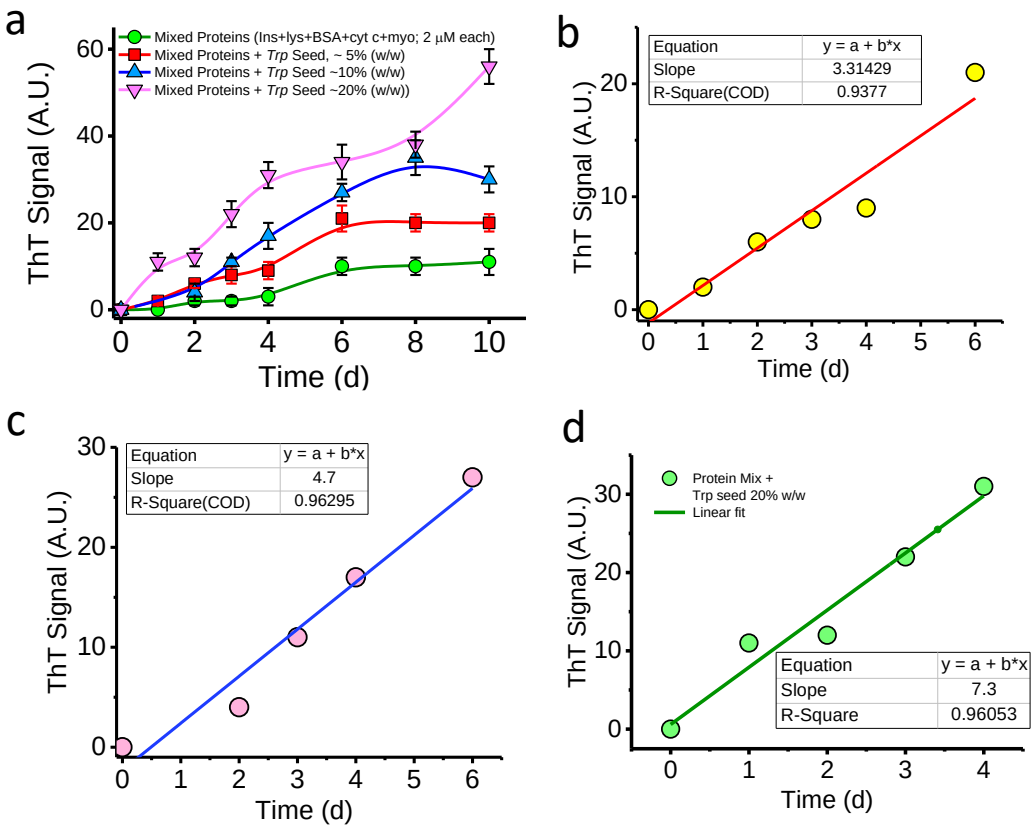


Figure S5. **Analysis of the rate of Trp-seeded coaggregation a protein mixture in a dose-dependent manner.** ***a,*** Thioflavin-T data showing coaggregation of different globular proteins in the presence of different doses of *Trp*-seeds, as labelled. ***b,*** linear fit of initial time points of the coaggregation reaction at 5 % w/w seed of *Trp*. ***c,*** linear fit of initial time points of the coaggregation reaction at 10 % w/w seed of *Trp*. ***d,*** linear fit of initial time points of the coaggregation reaction at 20 % w/w seed of *Trp*.

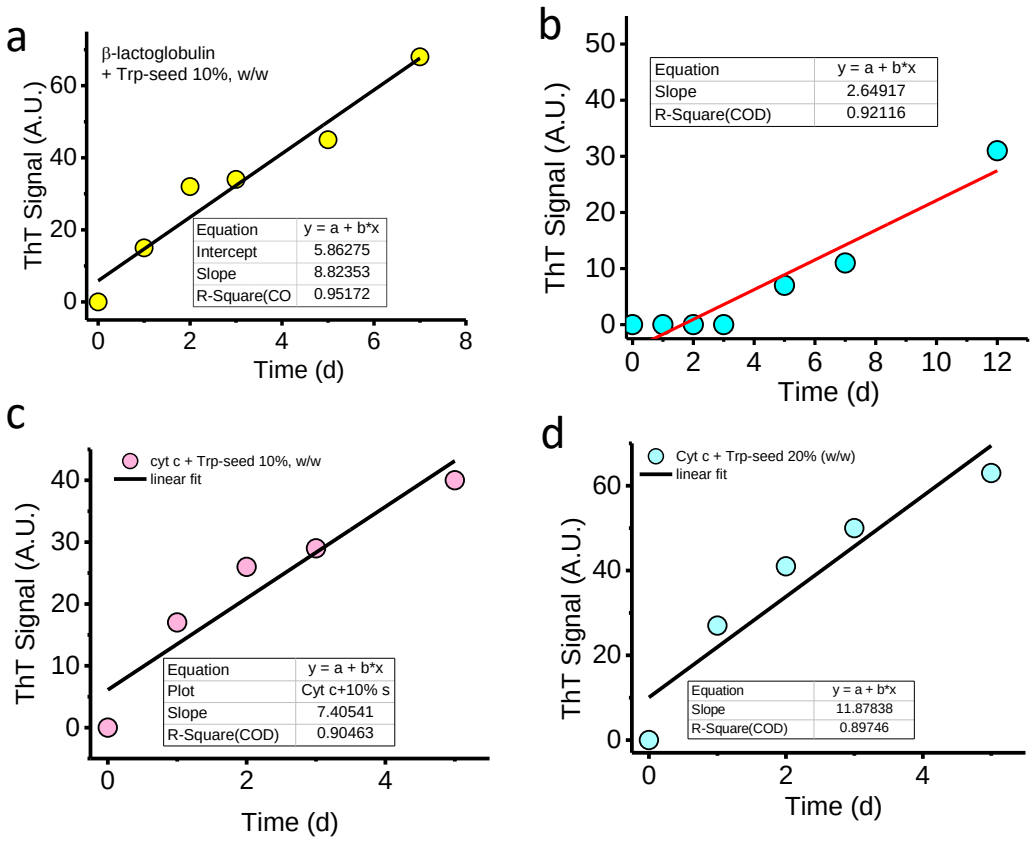
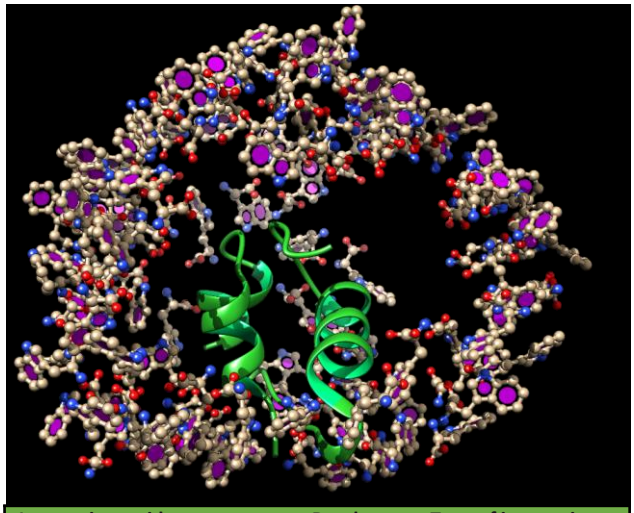


Figure S6. Analysis of the rate of aggregation of β-lactoglobulin and cytochrome c in the prdopamine in the presence of Trp-nanostructures. ***a,*** linear fit of initial time points of the control aggregation reaction of β-lactoglobulin. ***b,*** linear fit of initial time points of the aggregation reaction of β-lactoglobulin in the presence of 10 % (w/w) *Trp* seeds. ***c,*** linear fit of initial time points of the aggregation reaction of cytochrome c at 10 % w/w seed of *Trp*. ***c,*** linear fit of initial time points of the aggregation reaction of cytochrome c at 20 % w/w seed of *Trp*.

a

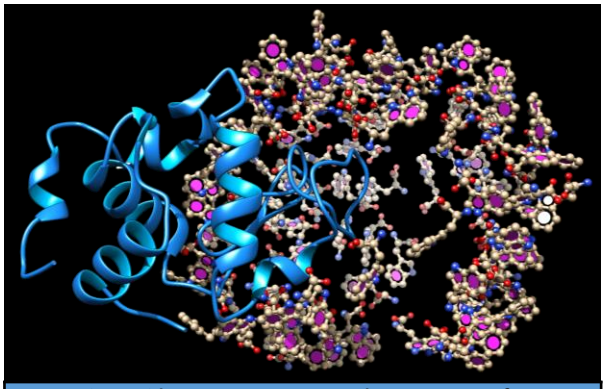
Trp nanostructure – Insulin



Interacting residue	Bond length (Å)	Type of interaction
C:TRP7:O1 - B:TYR26:OH	2.6	Hydrogen Bond
C:TRP26:O1 - B:PHE24:O	3.0	Hydrogen Bond
C:TRP42:O1 - A:GLU17:OE1	2.3	Hydrogen Bond
C:TRP63:O1 - B:TYR16:OH	3.0	Hydrogen Bond
C:TRP26:N4 - A:ASN21:ND2	3.2	Hydrogen Bond
C:TRP77:O1 - B:PHE24:N	3.2	Hydrogen Bond
C:TRP7:O2 - B:TYR26:OH	2.9	Hydrogen Bond
C:TRP26:C8 - B:PHE24:O	3.1	Hydrogen Bond
C:TRP82:C10 - A:GLU17:O	3.7	Hydrogen Bond
C:TRP77:O1 - B:GLY23:CA	3.0	Hydrogen Bond
C:TRP34 - A:GLY1:N	3.0	Hydrogen Bond
C:TRP34 - A:GLU4:OE1	4.6	Pi-Anion
C:TRP34 - A:GLU4:OE1	4.6	Pi-Anion
C:TRP32 - B:THR27:CG2	3.3	Pi-Sigma
C:TRP32 - B:PHE25	5.3	Pi-Pi Stacked
C:TRP11 - B:LYS29	4.5	Pi-Alkyl
C:TRP60 - B:PRO28	4.7	Pi-Alkyl

b

Trp nanostructure – Lysozyme

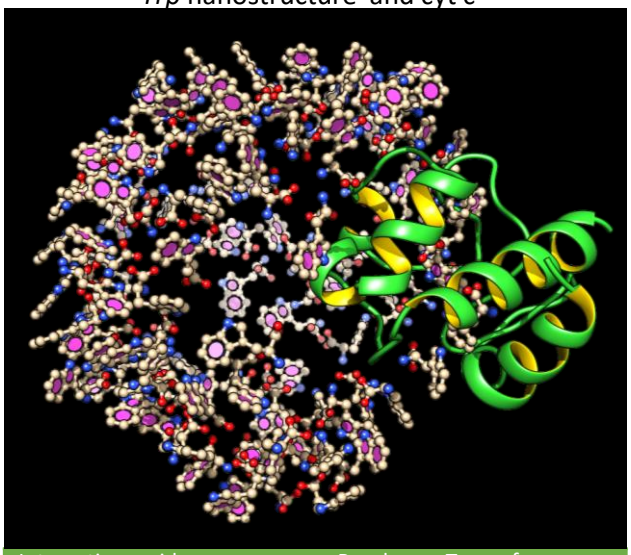


Interacting residue	Bond length (Å)	Type of interaction
B:TRP73:N4 - A:GLU35:OE1	2.8	Hydrogen Bond
B:TRP10:O2 - A:THR43:OG1	3.1	Hydrogen Bond
B:TRP70:O2 - A:ASN44:ND2	2.8	Hydrogen Bond
B:TRP40:O2 - A:THR47:OG1	2.6	Hydrogen Bond
B:TRP45:N3 - A:THR47:OG1	2.8	Hydrogen Bond
B:TRP94:N3 - A:SER81:OG	3.0	Hydrogen Bond
B:TRP18:O2 - A:ASN103:ND2	3.0	Hydrogen Bond
B:TRP70:C10 - A:ASN44:OD1	2.6	Hydrogen Bond
B:TRP28:O2 - A:TRP63	3.5	Hydrogen Bond
B:TRP94 - A:SER81:OG	3.7	Hydrogen Bond
B:TRP31 - A:ILE98:CG2	3.2	Pi-Sigma
B:TRP31 - A:ALA107	3.3	Pi-Alkyl
B:TRP73 - A:VAL109	4.3	Pi-Alkyl
B:TRP76 - A:ALA42	4.3	Pi-Alkyl
B:TRP83 - A:LEU84	5.4	Pi-Alkyl
B:TRP83 - A:LEU84	5.0	Pi-Alkyl
B:TRP93 - A:PRO79	4.6	Pi-Alkyl
B:TRP93 - A:PRO79	4.3	Pi-Alkyl
B:TRP94 - A:PRO79	4.8	Pi-Alkyl
B:TRP94 - A:ALA82	4.2	Pi-Alkyl
B:TRP31 - A:TRP108	5.1	Pi-Alkyl
B:TRP31 - A:TRP108	5.2	Pi-Alkyl

Figure S7 Rigid body Z-Docking analysis reveals direct interaction between *Trp*-nanostructure with globular proteins. ***a,*** Insulin (PDB ID: 3I3Z) and *Trp*-nanostructure. ***b***, Lysozyme (PDB ID: 5WRA) and *Trp*-nanostructure.

a

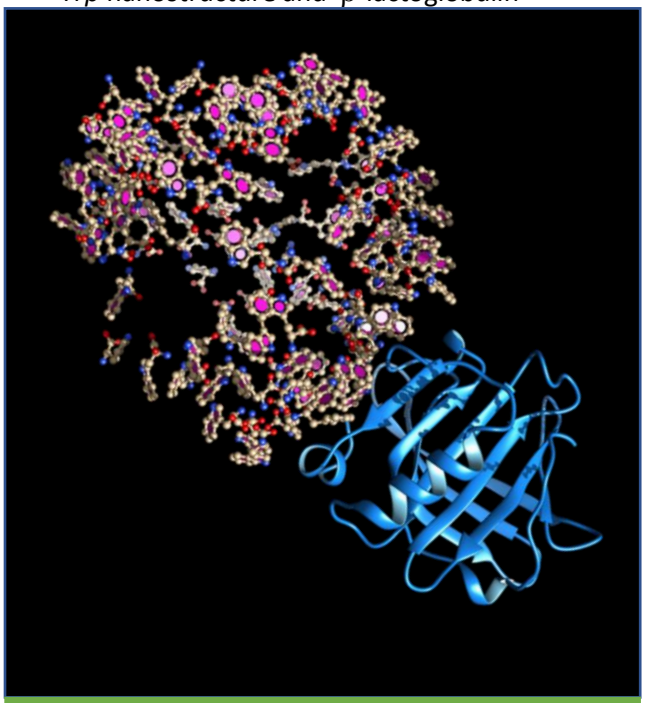
Trp nanostructure and cyt c



Interacting residue	Bond length (Å)	Type of interaction
B:TRP29:N4 - A:THR58:O	2.6	Hydrogen Bond
B:TRP31:O1 - A:GLU66:OE2	2.7	Hydrogen Bond
B:TRP41:O1 - A:THR40:O	3.0	Hydrogen Bond
B:TRP93:N4 - A:TRP59:NE1	2.3	Hydrogen Bond
B:TRP29:O1 - A:LYS60:NZ	2.8	Hydrogen Bond
B:TRP96:O1 - A:LYS79:NZ	3.3	Hydrogen Bond
B:TRP52:N4 - A:ALA83:N	3.0	Hydrogen Bond
B:TRP93:C8 - A:ASN52:OD1	3.5	Hydrogen Bond
B:TRP93:C10 - A:ASN52:OD1	2.7	Hydrogen Bond
B:TRP96:C8 - A:THR47:OG1	2.4	Hydrogen Bond
B:TRP96:O1 - A:THR47:CB	3.0	Hydrogen Bond
B:TRP92:O2 - A:LYS53:CE	2.4	Hydrogen Bond
B:TRP29:N4 - A:LYS60:CE	2.4	Hydrogen Bond
B:TRP83:O2 - A:MET80:CA	3.3	Hydrogen Bond
B:TRP41:N3 - A:TYR48	4.9	Pi-Cation
B:TRP83 - A:PHE82	4.2	Pi-Pi Stacked
B:TRP83 - A:LYS13	5.2	Alkyl
B:TRP94 - A:CYS14	5.0	Alkyl
B:TRP52 - A:ILE81	4.9	Pi-Alkyl
B:TRP63 - A:PRO44	4.7	Pi-Alkyl
B:TRP63 - A:PRO44	3.7	Pi-Alkyl
B:TRP83 - A:CYS14	5.2	Pi-Alkyl
B:TRP83 - A:CYS17	4.6	Pi-Alkyl
B:TRP93 - A:PRO30	3.5	Pi-Alkyl
B:TRP93 - A:LEU32	5.0	Pi-Alkyl
A:PHE82 - B:TRP83	4.6	Pi-Alkyl

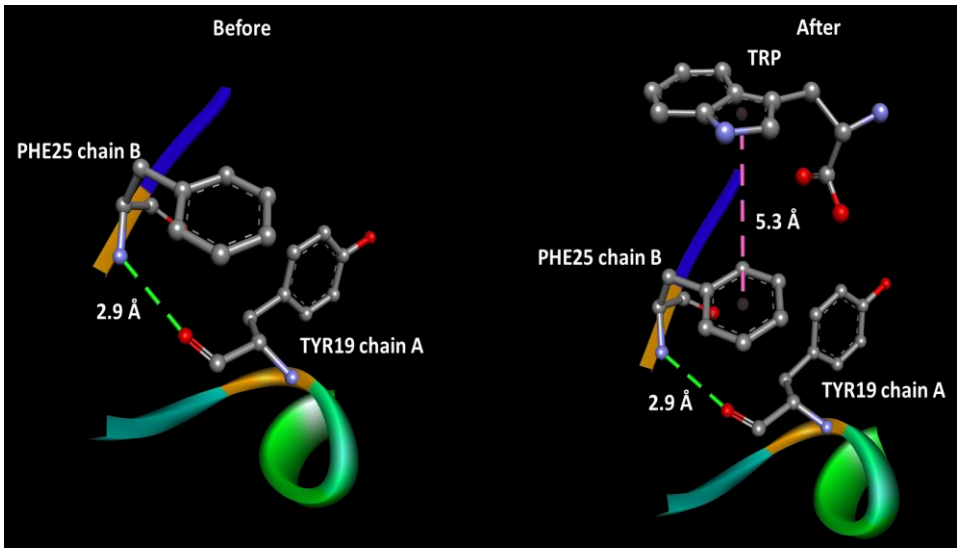
b

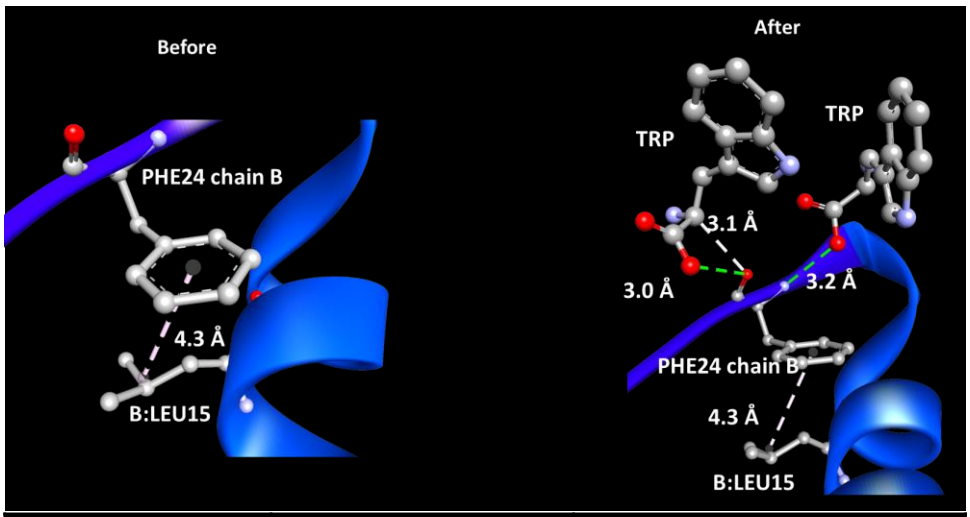
Trp nanostructure and β-lactoglobulin



Interacting residue	**Bond length (Å)**	**Type of interaction**
B:TRP61:O1 - A:GLN155:NE2	2.8	Hydrogen Bond
B:TRP69 - A:ALA34:CB	3.4	Pi-Sigma
B:TRP14 - A:ILE162:CD1	3.7	Pi-Sigma
B:TRP67 - A:PHE151	4.5	Pi-Pi T-shaped
B:TRP67 - A:PHE151	4.2	Pi-Pi T-shaped
B:TRP61 - A:ILE162	5.1	Alkyl
B:TRP14 - A:ILE162	3.5	Pi-Alkyl
B:TRP19 - A:ALA34	5.3	Pi-Alkyl
B:TRP47 - A:ILE29	4.5	Pi-Alkyl
B:TRP49 - A:ILE29	5.4	Pi-Alkyl
B:TRP49 - A:ILE29	4.4	Pi-Alkyl
B:TRP61 - A:ILE162	5.0	Pi-Alkyl
B:TRP67 - A:LEU149	4.7	Pi-Alkyl
B:TRP69 - A:ALA34	4.4	Pi-Alkyl
B:TRP70 - A:ILE162	5.4	Pi-Alkyl
B:TRP61 - A:TRP61	4.3	Pi-Alkyl

Figure S8 Rigid body Z-Docking analysis reveals direct interaction between *Trp*-nanostructure with globular proteins. ***a,*** Cytochrome c (PDB ID: 1HRC) and Trp-nanostructure. ***b,*** β-lactoglobulin (PDB ID: 5I05) and *Trp*-nanostructure.





Interacting residues of Ins	Interaction within Insulin	Interaction with TRP nanostructure
B:PHE25	Hydrogen Bond (A:TYR19)	Hydrogen Bond (A:TYR19) Pi-pi stack (TRP)
B:PHE24	Pi-Alkyl (B:LEU15)	Pi-Alkyl (B:LEU15) Hydrogen Bond Hydrogen Bond Hydrogen Bond

Figure S9. Analysis of the *Phe* 25 and *Phe* 24 of insulin's B-chain before and after docking reveals formation of three additional H-bonds after the complex formation with *Trp*-nanostructure, as labelled.

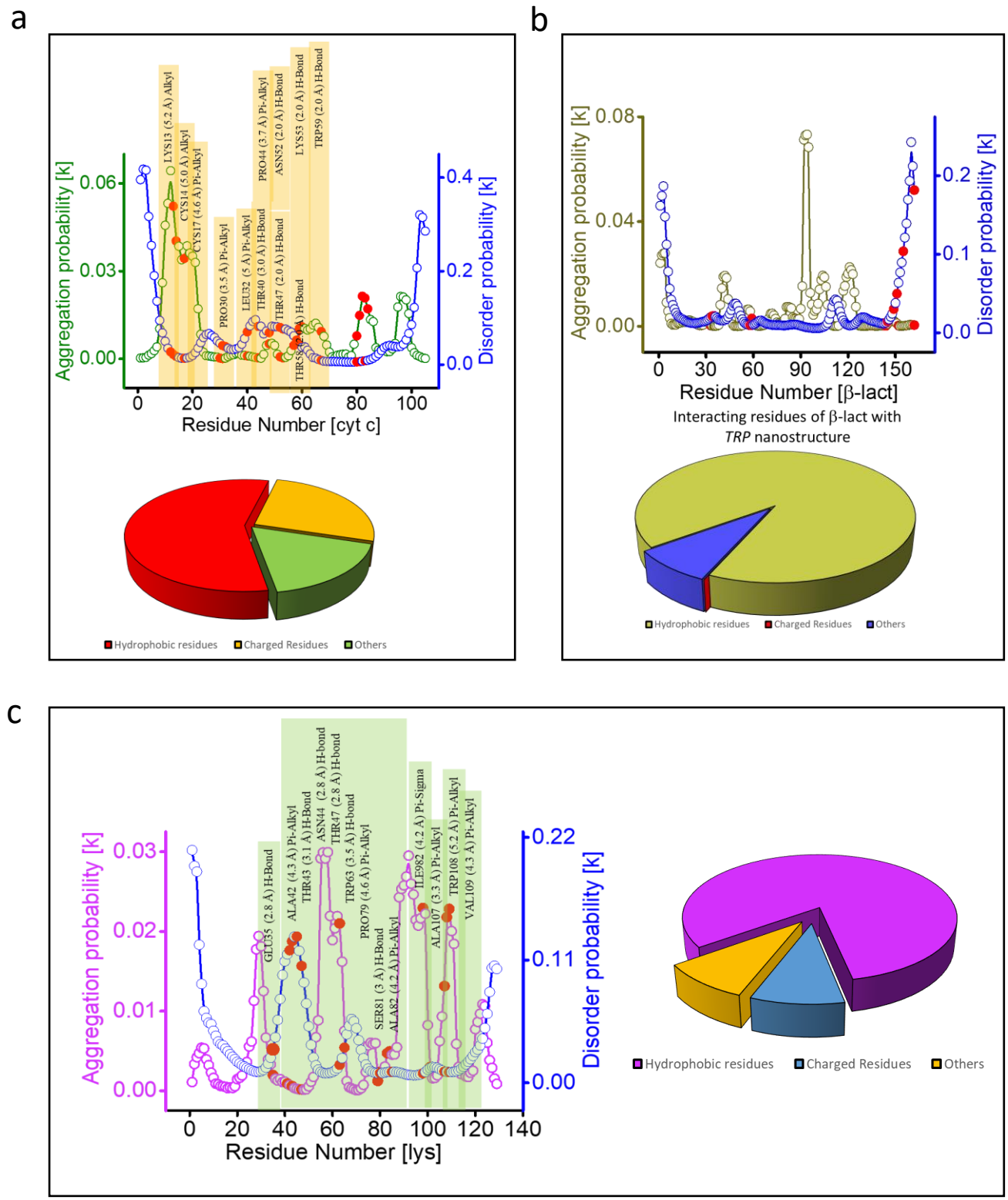


Figure S10 Sequence analysis of proteins using PASTA 2.0: (blue curve) degree of disorderedness; (magenta curve) Aggregation probability of the protein. Yellow shaded region displays the amino acids (●) which interact with the *Trp* nanostructure and the type of non-covalent contacts. ***a,*** Cytochrome c ***; b,*** β-lactoglobulin; ***c,*** Lysozyme. Inset pi-chat (shown in a-c) reveals major contribution of both electrostatic and hydrophobic residues for a viable interaction between the respective proteins and *Trp* nanostructure.

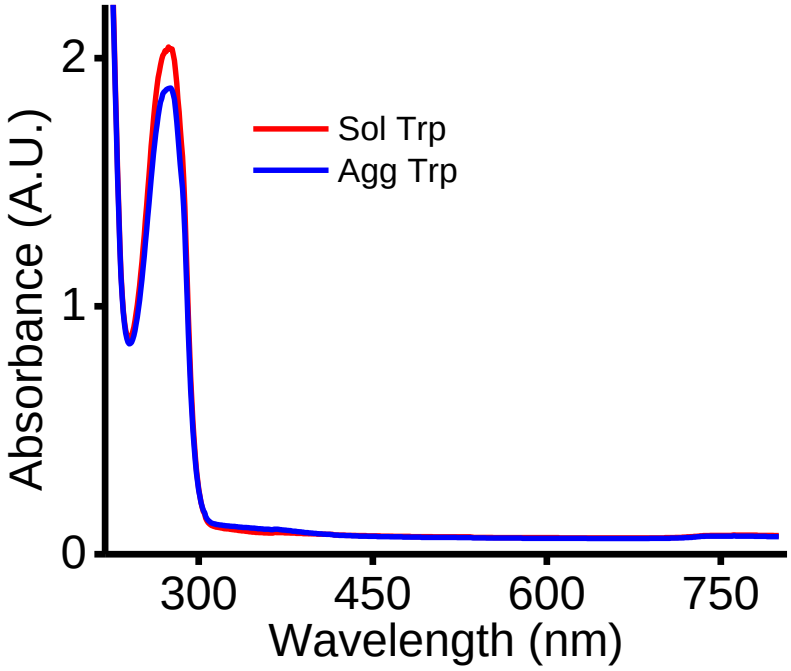


Figure S11 UV-visible absorption data for Trp sample before and after aggregation, as labelled.

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